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Hypercalcemia and Hypocalcemia

THEODORE B. SCHWARTZ
ROBERT N. HEDGES, JR.

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Hypercalcemia and Hypocalcemia

THEODORE B. SCHWARTZ
ROBERT N. HEDGES, JR.

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THE IDEAL (AND UNATTAINABLE) GOAL to which the practicing physician aspires is to describe a patient's illness entirely in terms of its pathogenetic mechanisms. He would then be in a position, not only to observe, but to predict and prevent symptoms. The appropriate diagnostic procedures could be interpreted with ease, and rational therapy would be self-evident. Clearly, this state of grace has not been approached in the field of calcium metabolism, and a discussion dealing with the clinical manifestations of hyper- and hypocalcemia has disadvantages already obvious to the basic scientist. He reminds us that significant changes in calcium metabolism may be taking place while serum calcium concentrations remain in the normal range. He also points out the fallacy inherent in a classification based on the measurement of

total serum calcium, a value divisible into at least three fractions of physiologic importance (4).

Despite these deterrents, it is our conviction that a review of the disorders of calcium metabolism, based on the findings of hyper- or hypocalcemia, has considerable merit. While recognizing the limitations of such a review, we submit that the determination of the total serum calcium level (which is the *only* calcium measurement available to most physicians) is a most helpful and reliable procedure. Indeed, it may be the first significant clue to the solution of a perplexing diagnostic problem. After a period of relative dormancy, this field is rapidly expanding, and so it seems a propitious time to organize the presently available observations into a classification based on pathophysiologic mechanisms. This classification should not only serve to categorize documented aberrations in serum calcium concentration but should also provide a framework for the incorporation of new findings as they emerge.

DEFINITIONS

The range of the normal variation of serum calcium is difficult to delimit, depending, as it does, on the method used for its determination. For this reason, it is essential that the physician acquaint himself with the range of values found to be normal in his own clinical laboratory. It has been customary, in the past, to consider serum calcium levels between 9 and 11.0 (or even 11.5) mg. % as normal. However, newer technics and wider experience have led to the conclusion that these values are too high; and so, in this presentation, serum calcium levels *above 10.5 mg. %* define the state of hypercalcemia, while those *below 8.5 mg. %* are indicative of hypocalcemia.

PHYSIOLOGIC CONSIDERATIONS

Of the total serum calcium, 60% exists as the ion, Ca^{++}, uncomplexed with serum proteins or organic anions, such as citrate. Again it is emphasized that it is the ionized fraction which exerts the major physiologic effects, although it is the total serum calcium which is usually determined. Ca^{++}, in appropriate amounts, is necessary for such diverse activities as synaptic and neuromus-

cular transmission, gastric secretion, renal tubular reabsorption of water and coagulation of blood. In effect, it appears that Ca^{++} is essential in preserving the normal function of the cell membrane and has an important influence on the transport of other ions across cell surfaces. These activities, however, are dependent not only on Ca^{++} concentration but also on the total ionic environ-

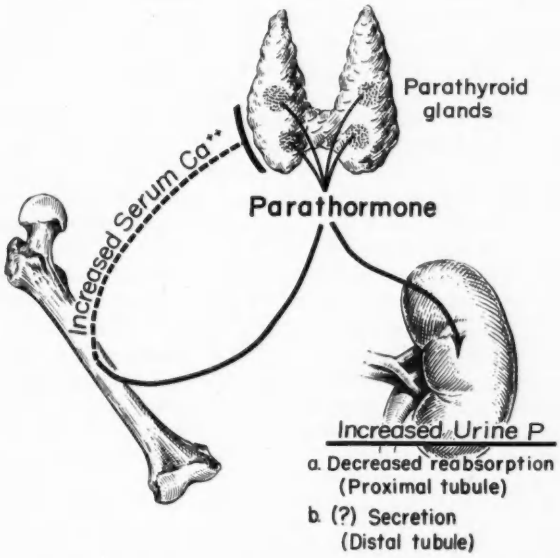

FIG. 1.—Principal effects of Parathormone (parathyroid hormone).

ment, including plasma constituents, such as hydrogen (pH), potassium, magnesium, phosphate and citrate. Quantitative changes in these latter factors may strongly influence the manifestations usually seen in hyper- or hypocalcemic states. Thus, the symptoms of hypocalcemic tetany may be minimized or abolished in the presence of potassium deficiency, while hypomagnesemia may precipitate profound tetany in the presence of normocalcemia.

Calcium concentrations are maintained in body fluids by the

balance between intake from the gut and extraction from the huge reservoir in bone, on the one hand, and excretion through the kidney and large bowel and deposition in bone, on the other. Finer control of serum calcium levels is effected primarily through the influence of the parathyroid glands, although there is evidence ascribing secondary roles to growth, thyroid, adrenal and gonadal hormones.

Parathyroid hormone, a small protein which has recently been obtained in pure form, has two major actions, as indicated in Figure 1. First, it increases the rate of breakdown of bone, releasing calcium into the plasma and extracellular fluid; and second, it increases the excretion of phosphate in the urine, either through decreasing proximal renal tubular reabsorption or increasing distal tubular secretion.

The relation between Ca^{++} and the parathyroid glands serves as a classic example of a self-regulating or "feed-back" mechanism. The crux of this relationship is the fact that *Ca^{++} inhibits parathyroid activity.* It follows, then, that, if for any reason serum Ca^{++} is increased, parathyroid hormone release will be depressed, less Ca^{++} will be dissolved from bone and serum Ca^{++} will tend to fall to normal levels. Should serum Ca^{++} tend to fall, the converse sequence of events occurs. Finally, since considerable phosphate is released from dissolved bone, the second action of parathyroid hormone permits the excretion of the excess phosphate, thus maintaining the normal serum phosphate level.

Some of the foregoing relationships are amplified in the subsequent discussion, but a full review is beyond the scope of this report.

THE CLINICAL PICTURE IN HYPERCALCEMIA

SYMPTOMS:

Weakness	Dry mouth	Drowsiness
Fatigue	Bitter taste	Lethargy
Anorexia	Pruritus	Failing memory
Nausea	Polydipsia	Confusion
Vomiting	Polyuria	Change in personality
Abdominal pain	Bone pain	Psychotic behavior
Constipation	Blurred vision	Stupor and coma
Dysphagia	Impaired hearing	

Recently, Randall and Keating (14) reported on the serendipity inherent in the diagnosis of hyperparathyroidism, a classic form of hypercalcemia. The ambiguity, the nonspecificity or the complete absence of the symptoms of hypercalcemia was underlined by the fact that in 9 out of 20 patients an initial impression of *hypocalcemia* was proposed.

In the list of the major symptoms of hypercalcemia (p. 6), it can be easily seen that none are pathognomonic. Yet, their *occurrence together* in a patient who might have cause for hypercalcemia must be regarded as highly suspicious.

The symptoms of weakness, dysphagia and constipation are due to the hypotonicity of the smooth and skeletal muscles, which probably also occurs in the myocardium. The gastrointestinal complaints of anorexia, nausea and vomiting are thought to be central in origin. With the consequent renal damage resulting from hypercalcemia, these same gastrointestinal symptoms may be reinforced by renal failure.

The abdominal pain of hypercalcemia can be generalized and nonspecific, or localized, as when produced by peptic ulcer. The latter condition is found with increased frequency in patients with hyperparathyroidism (males, 28.6%; females, 4.6%). There is some evidence that both excessive parathyroid hormone and hypercalcemia per se may produce adverse affects on the gastric secretion and the gastrointestinal mucosa. The renal pain of nephrolithiasis is usually characteristic and should serve as a reminder to check the serum calcium in all patients with calcium-containing stones.

The renal tubules are affected specifically by excessive Ca^{++}, so that reabsorption of water is impaired, with resultant polyuria and polydipsia. It is worth noting that the combination of thirst and polyuria is always abnormal, for in physiologic states any stimulus-provoking thirst usually produces oliguria.

The skeletal symptoms are due mainly to the physical changes in the bone as reflected in the pain-sensitive periosteum. The symptoms related to the central nervous system show a wide range of severity, from mild drowsiness to profound and life-endangering coma. This latter state, referred to as "hypercalcemic crisis," requires emergency therapy, just as diabetic acidosis and adrenal crisis do.

PHYSICAL SIGNS:

Cardiac arrhythmias	Hypotonicity of muscles
Failure to grow (infants)	Hyperextensible joints
Pigeon-breast deformity	Depressed or absent reflexes
"Elfin" facies	Transient facial palsies
Conjunctival deposits	Tender and atrophic muscles (myopathy?)
Band keratitis	Ocular muscle disturbances
Corneal calcification	Elevated blood pressure
Bone tenderness	Tachycardia
Pathologic fractures of bone	Bradycardia

Characteristic signs attributable to the elevation of serum calcium alone are neither pathognomonic nor abundant. However, as in the symptomatology of this entity, when present in a group they should arouse suspicion. The neuromuscular system may provide clues to the diagnosis of hypercalcemia, with manifestations of depressed muscle action such as the hypotonicity of muscles, hyperextensible joints, depressed or absent reflexes and transient facial palsies. Evidence of myopathy, with tenderness and weakness of muscles, has been specifically correlated with high levels of serum calcium in a few patients.

Complete recovery has been produced by various methods of lowering the calcium level, only to recur if the calcium is allowed to rise.

In the cardiovascular system, an elevated blood pressure may be found. This may be related to early nephrocalcinosis, and it also may be reversible if therapy is started soon enough. Tachycardia, bradycardia and a number of cardiac arrhythmias have been observed.

The eye signs of hypercalcemia represent an interesting type of ectopic calcification and may be noted in the conjunctiva, subconjunctiva or cornea (in the latter, a slit lamp is a valuable aid in the diagnosis). A characteristic type of band keratopathy, due to calcium deposition, occurs in a thin line running concentrically with the limbus and resembles arcus senilis. Differentiating features include: a clear zone in the cornea between the calcium and the sclera, and a maximal amount of deposition of the calcium in the medial and lateral portions of the sclera. This deposition tends to be patchy and hazy, with the most dense portions in the periph-

ery. The importance of finding this type of ectopic calcification is emphasized by the fact that it may represent the only positive evidence of a previous hypercalcemia when the serum calcium is reduced to normal because of secondary renal damage. The conjunctival deposits are small, dull white flecks usually present over the sclera but occasionally located on the inner surface of the eyelids.

One of the characteristic findings of hypercalcemia in infancy is usually described as a failure to thrive. This has included both mental and physical retardation and the appearance of an "elfin" facies.

As further growth occurs, albeit slowly, features such as microcephaly and pigeon-breast deformity may be noted. The possibility exists that a considerable number of adults have previously had mild "idiopathic" hypercalcemia in infancy and later recovered, with the persistence of some of these stigmata.

X-RAY FINDINGS.—The abnormalities of bone seen in patients with hypercalcemia may vary extensively, depending on the underlying etiology. X-ray lesions of hypercalcemia in patients with no primary bone disease are usually related to various forms of bony demineralization. This may be generalized, or may be localized, as in bone cyst formation and loss of the lamina dura. In hypercalcemic children, the epiphyses may show an increased density while the ends of the bones reveal transverse bands of increased density. A premature craniosynostosis may also occur.

Ectopic calcification is another prominent x-ray finding in hypercalcemia. This can occur in almost any soft-tissue location, such as the muscles, the blood vessels and the eyes; but the kidneys are particularly susceptible. The roentgenogram may show evidence of renal calculi, nephrocalcinosis or both.

Nephrocalcinosis, appearing as small aggregations of calcium in the papillary areas, is strongly suggestive of hypercalcemia, past or present.

ELECTROCARDIOGRAPHIC FINDINGS.—Hypercalcemia produces a marked shortening of the Q–T interval, which is generally followed by a prominent U wave. The shorter interval is due mainly to a decrease in the S–T segment. Various types of arrhythmias may occur.

THE CLINICAL PICTURE IN HYPOCALCEMIA

SYMPTOMS:

Numbness and tingling of the hands, feet, mouth and tongue	Irritability
Fatigue	Anxiety
Stiffness of muscles	Inability to concentrate
Muscular aches and cramps	Mental retardation
Carpal-pedal spasm	Psychosis
Tonic and clonic convulsions	Palpitation
Syncope or unconsciousness	Voice changes
Headache	Attacks of choking (laryngeal stridor)

The classic picture of acute hypocalcemia is best exemplified by tetany; the chronic state may be more variable. Although the symptoms of the nervous and muscular systems in hypocalcemia have a common denominator (the requirement for physiologic concentrations of calcium ion for proper synaptic function), their variation and range of intensity is quite broad. The important point is to pursue even minor degrees of numbness and paresthesias, which may often be passed off as manifestations of nervous tension, vitamin deficiencies and the like. The classic manifestations of numbness and the "pins-and-needles" sensations of the hands, feet and about the mouth, together with muscle cramps, stiffness or frank carpal-pedal spasm, are pathognomonic of a low ionized calcium in the serum. Most commonly this is caused by the "hyperventilation syndrome," but it is incumbent on the physician to be certain that a more serious defect is not present. Less intense symptoms, such as fatigue, muscle weakness, mild paresthesias and nervousness, may represent a slight lowering of the ionized calcium level without affecting the total calcium in the blood.

Perhaps the most dramatic symptoms of hypocalcemia are those which produce the central nervous system manifestations of unconsciousness, syncope and convulsions. These may occur repeatedly in patients who have never complained of the more obvious symptoms of tetany. A variation of this clinical picture is the occurrence of a sudden episode of laryngeal spasm, which then produces hypoxia and unconsciousness. Milder degrees of laryngeal constriction may be mistaken for asthma or the dyspnea of

cardiac failure. Emotional disturbances, including frankly psychotic behavior, may also result from hypocalcemia.

PHYSICAL SIGNS:

Subcapsular cataracts
Hyperkeratosis and dry skin
Brittleness of the nails
Longitudinal ridging of the nails
Alopecia
Carpal-pedal spasm
Positive Chvostek's sign
Positive Trousseau sign
Distorted and deficient tooth formation in children
Papilledema (pseudotumor cerebri)

In the acute phase, the physical signs of hypocalcemia are related to the increased nervous and muscular irritability. Muscular relaxation is not normal, and there is an exaggerated response to active and passive motion and to mechanical stimulation, such as that produced with the Chvostek sign. This is elicited by gently tapping the facial nerve in the preauricular area. A positive sign indicating hypocalcemia is detected by a spasmodic contraction of the facial muscles about the mouth, nose and eye on the homolateral side. A comparable sign is that of Trousseau, in which compression of the brachial artery for from 1 to 5 minutes will produce spasm of the muscles of hand and wrist, often resulting in the typical "main d'accoucheur." Frequently, mild hyperventilation of the patient will produce paresthesias and carpal-pedal spasm.

Many of the other signs of hypocalcemia are those related to a long-standing defect resulting in abnormalities of a large portion of the ectodermal structures, such as the skin, nails, hair, teeth and lenses. Cataracts appear with sufficient regularity to justify ordering a serum calcium evaluation in all such patients below age 50. In some respects, the patients with chronic hypocalcemia may suggest the presence of a genetic defect; and, in fact, the patient with pseudohypoparathyroidism does combine a genetic abnormality with that of hypocalcemia.

Finally, in rare instances, chronic depression of the serum calcium level may produce increased intracranial pressure with papilledema and other manifestations, which will disappear when the normocalcemic state is restored.

X-RAY FINDINGS.—Patients with long-standing idiopathic hypo-

parathyroidism or pseudohypoparathyroidism frequently reveal stippled areas of calcification in the basal ganglia. Occasionally, ectopic calcification may occur in the soft tissues of the fingers as well. An unusual and rather paradoxical roentgenographic finding in these patients is bony demineralization. In children, tooth structure may be distorted and incomplete.

ELECTROCARDIOGRAPHIC FINDINGS.—Hypocalcemia produces an increase in the Q–T interval, owing to a lengthening of the S–T segment. This represents an increase in the duration of mechanical systole of the heart, in contrast to the hypokaliemic states, where the electrical systole is prolonged but the mechanical systole is normal.

CLASSIFICATION

In Tables 1 and 2, classifications of the various factors in the genesis of hyper- and hypocalcemia are outlined. An effort has been made to group disease entities in categories indicating the predominant pathophysiologic alteration. These, like all clinical classifications, are necessarily limited by an imperfect understanding of the etiologic influences and the likelihood that, in many instances, more than one abnormality exists. Nevertheless, we feel that an orderly listing of those diseases known to be associated with abnormal values of the serum calcium is helpful to the practicing physician in his efforts to make an accurate diagnosis and to institute rational therapy. The list is not all-inclusive, since it consists of only those disorders in which the occurrence of an abnormal serum calcium level has been reasonably well documented.

TABLE 1.—HYPERCALCEMIA

I. Increased intestinal absorption of calcium
    1. Milk and alkali syndrome
    2. Vitamin D intoxication
    3. Sarcoidosis (? vitamin D sensitivity)
    4. Hypercalcemia of infancy (? vitamin D sensitivity)

II. Increased bone resorption
    A. Endocrinopathy
        1. Hyperparathyroidism
            a) Primary

TABLE 1 (*Cont.*)

(1) Adenoma
(2) Idiopathic hyperplasia
(3) Carcinoma
b) Secondary
(1) Chronic renal insufficiency
2. Hyperthyroidism
B. Malignancy
1. Tumors involving bone marrow
2. Tumors metastatic to bone
a) Untreated
b) Induced by treatment
3. Tumors sparing bone
C. Bone dysplasia
1. Paget's disease of bone
2. Polyostotic fibrous dysplasia
III. Decreased bone synthesis
1. Acute osteoporosis of disuse
2. Adrenal insufficiency
a) Absolute (Addison's disease)
b) Relative
(1) Postoperative Cushing's syndrome
(2) Adrenocorticoid withdrawal

TABLE 2.—HYPOCALCEMIA

I. Decreased intestinal absorption of calcium
A. Vitamin D deficiency
1. Simple rickets
2. ? Vitamin D–resistant rickets
B. Malabsorption syndrome
1. Intrinsic intestinal defect
2. Biliary obstruction
3. Intestinal shunt
4. Intestinal rapid transit
II. Decreased bone resorption
1. Hypoparathyroidism
a) Primary
b) Pseudohypoparathyroidism
c) Postsurgical
(1) Total removal of the parathyroids
(2) Partial removal or damage to the parathyroids
(3) Removal of parathyroid tumor
d) Infantile tetany

TABLE 2 (*Cont.*)

III. Increased bone synthesis ("hungry bones")
  1. Removal of parathyroid tumors
  2. Osteoblastic metastatic bone disease

IV. Increased calcium loss
  A. Renal wasting of calcium
    1. Renal tubular acidosis
    2. Fanconi syndrome
    3. "Phosphate diabetes" (vitamin D–resistant rickets)
  B. Complex formation
    1. Acute pancreatitis
    2. Chelate administration
      a) Multiple transfusions containing citrate
      b) Infusion of disodium ethylene diamine tetracetate (NaEDTA)
    3. Hypoproteinemia
    4. Chronic renal insufficiency (uremia)

HYPERCALCEMIA

It is evident that hypercalcemia will result when the rate of entry of calcium into the serum exceeds its rate of removal. It is not surprising that disorders resulting in increased absorption of calcium from the gut, or enhanced dissolution of bone, may lead to elevation in serum calcium levels. Similarly, a sharp reduction in the mineralization of bone, at a time when the calcium intake is unimpeded, may also provoke hypercalcemia. Theoretically, an impaired excretion of calcium, or an increased calcium-binding capacity of serum, should also result in serum calcium elevations. However, there is, as yet, no evidence that these latter mechanisms are clinically important, although decreased excretion of calcium through the gut is probably a factor in the pathogenesis of vitamin D intoxication. Hyperproteinemic states may result in mild hypercalcemia.

Generally, the ingestion of a diet high in calcium does not lead to hypercalcemia; the exception occurs when large amounts of sodium bicarbonate or other absorbable alkali are taken concurrently (*milk and alkali syndrome*), usually for self-medication of peptic ulcer. The correct diagnosis is gratifying, since discontinuance of the milk and alkali leads not only to a reversal of the hypercalcemia but also to considerable improvement in the often-

associated nephrocalcinosis. The use of large doses of vitamin D by "health addicts" and in the ill-advised therapy of osteoporosis in rheumatoid arthritis may produce hypercalcemia. Indeed, even when a rational indication exists, as in the treatment of hypoparathyroidism, the danger of *vitamin D intoxication* must be kept in mind, as illustrated in the following case report.

CASE 1.—*Vitamin D intoxication: postsurgical hypoparathyroidism.* J. B. (P.-St. L. H. #592303), was first seen at age 11 in March 1956 because of difficulty in controlling her hypoparathyroid state. Six months previously, she had been found to have a papillary adenocarcinoma of the thyroid with metastases to local lymph glands, and a bilateral radical neck dissection was performed. Past history revealed that the patient had had a series of x-ray treatments at age 4 for "sinusitis." Postoperatively, carpal-pedal spasm was controlled with calcium lactate and dihydrotachysterol, but the low serum calcium and elevated serum phosphorus levels persisted. For this reason, more intensive therapy was given, so that at the time of consultation the patient was taking 18 Gm. of calcium lactate and 100,000 I.U. of vitamin D, plus 120 mg. of desiccated thyroid daily. There was increasing polyuria and polydipsia, constipation and obvious lethargy. Her mouth constantly felt dry, with a bitter taste, and there were episodes of nausea and vomiting to a degree that, fortunately, made her incapable of retaining medication for the previous 2 days. Physical examination was unremarkable except for the semicomatose state and a pulse rate of 132. The diagnosis of calcium and vitamin D intoxication was borne out by serum calcium levels of 16.0 and 16.7 mg. % and a serum phosphorus level of 5.9 mg. %, and the blood nonprotein nitrogen (NPN) was 49 mg. %. An electrocardiogram revealed a shortened Q–T interval.

In addition to the discontinuance of calcium and vitamin D therapy, prednisone, 10 mg. every 8 hours, was begun; and fluid intake was increased to 3,000 ml. per day. Six days later, the serum calcium was 13.7 mg. %, and the azotemia had cleared; the patient appeared much improved and the vomiting had ceased. Prednisone dosage was gradually reduced, and after 2 weeks it was discontinued.

Comment.—This patient has been followed at monthly intervals up to the present time (November 1960), and her course has been similar to that of other parathyroprivic individuals. Particularly evident in younger patients are the inexplicable changes in calcium and vitamin D requirements, so that regular observation and determination of the serum levels of calcium and phosphate are

necessary to prevent alternating hypo- and hypercalcemia. It is our impression that a rapid growth phase increases the therapeutic requirements and that hypercalcemia appears if the increased dosage is maintained after the growth spurt has abated. The Sulkowitch test, a semiquantitative measure of urinary calcium, has not been a very helpful guide in our experience.

The widely promulgated notion that the appearance of hypercalcemia in patients with sarcoidosis results from involvement of bone is no longer tenable. Nor is it likely that this frequent complication (about one third of patients with active disease) (11) is merely a reflection of the hyperproteinemia associated with sarcoidosis. Rather, these patients behave metabolically as though they were intoxicated with vitamin D (6); and, indeed, they may, on occasion, appear to be unduly sensitive to small doses of this vitamin.

CASE 2.—*Hypercalcemia and sarcoidosis.*

A. W. (P.–St. L. H. #588056), in 1955, when she was 53, was referred by her personal physician because of fatigue, evening fever, cough and progressive weight loss. A roentgenogram of her chest revealed hilar adenopathy. Following hospitalization, the diagnosis of sarcoidosis was firmly established on the basis of skin and muscle biopsies as well as by hypergammaglobulinemia demonstrated by serum electrophoresis. In addition to the symptoms noted above, the patient had considerable nausea, anorexia and an inability to eat dry food. She drank large quantities of water, and urinated from 6 to 8 times each night. Serum calcium and phosphorus values were 14.4 and 5.3 mg. %, respectively. There was also clear-cut renal impairment, with diminished PSP excretion, blood NPN of 49 mg. % and a complicating urinary tract infection. Roentgenograms showed no evidence of nephrocalcinosis; but, surprisingly, a renal biopsy disclosed a heavy infiltration of sarcoid in the cortical parenchyma.

After some delay, prednisone therapy was instituted, with three objectives in mind: (1) to combat the generalized sarcoidosis, (2) to more specifically attack the renal lesions in the hope that they might be reversible and (3) to achieve a normocalcemic state. Antibiotics were administered concurrently to control the urinary tract infection. Results have been gratifying in that, 5 years later and with the patient still on small doses of adrenocorticoids, she is quite well. A repeat renal biopsy has reflected the considerable clinical improvement in renal function, and hypercalcemia has not recurred.

Idiopathic hypercalcemia of infancy, a puzzling malady characterized by a "failure to thrive," may be nothing more than still another manifestation of hypervitaminosis D. Since sensitivity to vitamin D is highly variable in a normal population, it remains problematical whether these infants suffer from some disturbance which increases their susceptibility to the effects of vitamin D. However, there is also a more severe form which does not respond to the usual treatment of discontinuance of vitamin D and the use of decalcified milk. The course is progressively downhill, and the patients usually die within the first few years of life.

The most common abnormality leading to hypercalcemia is accelerated breakdown of bone with the consequent liberation of calcium. Hyperparathyroidism serves as the classic example, since it represents an instance of a hormonally induced aberration of intrinsically normal bone. Studies with radioisotopes, such as calcium[45], have provided convincing evidence that both synthetic and resorptive rates (turnover) of bone are increased under the influence of excess parathyroid hormone. Serum calcium becomes elevated when the resorptive rate exceeds that of synthesis.

The diagnosis of *primary hyperparathyroidism* is often missed, or at least postponed, unless the typical clinical and biochemical findings are present. Much has been written (15) about the patient with suggestive historical but equivocal biochemical findings. In the case presented below, the reverse seems to have been true.

CASE 3.—*Parathyroid adenoma, osteitis fibrosa generalisata and postoperative hypocalcemia.*

S. D. A. (V. A. H., Hines, Ill.) was hospitalized in December 1958, at age 34, with the history of slowly progressive pain in the hips, knees and legs associated with weakness and weight loss for the previous 8 years. Consultation with various physicians led to several instances of hospitalization. Each time he was told that he had rheumatic disease, for which, 2 months before admission, he was given a course of adrenal steroids. In 1954, a "benign tumor" of the bone of the right ring finger was removed and, in 1958, he suffered a fracture of both bones of the left forearm, occurring after only mild exertion. One month before admission he was told that a radiographic study showed "some shadows in his kidneys."

Physical examination revealed a peculiar waddling gait, evidence of weight loss, a poorly defined mass in the area of right lower lobe of the

FIG. 2.—Tibial (*A*), metatarsal (*B*) and femoral (*C*) osteitis fibrosa generalisata (see Case 3).

thyroid gland, a pigeon-breast deformity (said to have developed during the past 5 years) and marked "clubbing" of the fingers, with short broad nails.

Preoperatively, serum calcium ranged between 12.6 and 16.2 mg. %; serum phosphorus, 2.2 and 2.7 mg. %; and alkaline phosphatase, 23 and 25 Bodansky units. Urine calcium (on a 200 mg. calcium diet) was 235–306 mg. per 24 hours (normal: less than 150 mg.). There was roentgenographic evidence of a nephrocalcinosis on the left side, but kidney function was only mildly impaired. X-ray examination of the bones showed striking changes (Fig. 2), characteristic of osteitis fibrosa gen-

eralisata. The percentage of renal tubular reabsorption of phosphate (%TRP)* ranged between 58 and 60 (normal: 80–95%).

The patient underwent a neck exploration in January 1959, and a large parathyroid adenoma (chief-cell type) was removed. Following surgery, both serum calcium and phosphate levels fell, so that by the tenth postoperative day they were 6.5 and 1.6. mg. %, respectively, while serum alkaline phosphatase remained elevated and %TRP rose to 100%. These dramatic changes occurred despite herculean measures taken to prevent them. The patient had been placed on a high calcium diet, supplemented with 30–39 Gm. of calcium gluconate and 13.5 mg. of dihydrotachysterol per day. He gradually responded, so that by the 25th postoperative day he had stabilized at serum calcium levels of 8.0–8.2 mg. %.

Comment.—This patient's spatulate fingers with short broad nails is a rare finding in primary hyperparathyroidism but one which has occurred even in the secondary variety (13).

It seems likely that energetic postoperative therapy spared this patient the serious consequences of the abrupt reversal in calcium metabolism. Hypocalcemia resulted from the removal of the bone-dissolving activity of parathyroid hormone, plus the greatly increased incorporation of calcium into the patient's "hungry bones." Indeed, it has become axiomatic that severe postoperative tetany is to be anticipated only in those patients in whom the hyperparathyroidism is accompanied by bone disease.

Parathyroid adenoma may be associated with recurrent calcific pancreatitis; apparently, calcification within the pancreatic ducts leads to this complication. In addition, as previously mentioned, hyperparathyroidism and peptic ulcer occur together with unexpected frequency. Finally, for reasons obscure to everyone, the parathyroids may participate in the syndrome of multiple endocrine adenomas, in which the islets of Langerhans, thyroid, pituitary and adrenals may be involved.

Idiopathic hyperplasia of the parathyroids and *parathyroid carcinoma* are rare causes of hyperparathyroidism. The clinical pic-

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* $\%TRP = \left(1 - \frac{\text{Urine } PO_4 \text{ conc.} \times \text{Serum creatinine}}{\text{Urine creatinine con.} \times \text{Serum } PO_4 \text{ conc.}}\right) \times 100$

It is low in hyperparathyroidism. For a fuller discussion of tests of parathyroid function, the reader is referred to a recent review by Schwartz (15).

ture may be indistinguishable from that of parathyroid adenoma, except that in hyperfunctioning parathyroid carcinoma, the symptoms and the blood chemical changes tend to be more severe.

In experimental animals, the removal of both kidneys has been found to be a most potent stimulus to the parathyroid glands, so that it is not surprising that patients with chronic renal insufficiency should be similarly affected. In the great majority of these cases, *parathyroid hyperplasia secondary to renal disease* is associated with hypocalcemia; but occasionally, hypercalcemia may supervene (13).

CASE 4.—*Hyperparathyroidism secondary to chronic glomerulonephritis.*

B. E. (P.–St. L. H. #601471), a white housewife, was admitted for the first time at age 55 in 1956, complaining of severe backache associated with joint pain, especially in the knees and ankles, of 8 years' duration. For the past 6 months she had been almost totally bedridden. A bone biopsy, obtained previously by an orthopedist, was said to be typical of osteitis fibrosa. On further questioning it became clear that the patient had had an attack of acute glomerulonephritis 15 years previously, with swelling of the legs and face, hematuria and hypertension. At age 52, she had noted progressive dimness of vision, which necessitated removal of cataracts bilaterally.

Physical examination showed only moderate obesity and dorsal kyphosis. Her bones were everywhere moderately tender to pressure.

Laboratory studies revealed isosthenuria, moderate proteinuria and a PSP excretion of 1.5 % in 15 minutes. She had azotemia (NPN of 94 mg. %) and metabolic acidosis (in mEq./L.: Na 150, Cl 112, CO_2 18.9 and K 4.4). Alkaline phosphatase was 25.8 units in the absence of liver disease, and %TRP was only 44. The serum calcium value was 10.0 mg. %, and serum phosphorus was 4.8 mg. %. Roentgen examination showed widespread severe demineralization of bone.

Our impression was that this patient had hyperparathyroidism and metabolic acidosis, secondary to chronic glomerulonephritis. She was treated initially with moderate amounts of calcium gluconate and vitamin D, in addition to Shohl's mixture (an alkalinizing solution containing 140 Gm. of citric acid, 75 Gm. of sodium citrate and 25 Gm. of potassium citrate per liter), 60 ml. per day. The acidosis was corrected, but the azotemia remained unchanged. Initially, the serum calcium value fell to 7.8 mg., but then it rose over a period of months to 12.6 mg. %. The calcium and vitamin D therapy was then discontinued, but calcium concentrations in the serum have remained repeatedly and consistently

between 11.2 and 12 mg. % for the past 2 years. Clinical improvement has been remarkable. The patient enjoys full activity, including fishing trips; and she remains free of pain; only relatively easy fatigability remains.

Comment.—Several questions regarding this patient remain unanswered. Was the initial diagnosis correct, or did this patient have primary hyperparathyroidism with secondary renal damage? The patient's history of nephritis and her dramatic improvement after therapy was instituted make the latter possibility unlikely. Has the constant stimulation of her parathyroid glands resulted, more recently, in the appearance of a parathyroid adenoma? This theoretic possibility cannot be discarded.

Hypercalcemia occurring during the course of *hyperthyroidism* has been well documented (9). It is found usually in the more severely affected patients and may be associated with radiologic evidence of bony demineralization. Symptoms reflecting the hypercalcemia are usually minimal or nonexistent, and they are overshadowed by those of the primary disorder; occasionally, they may be more severe. In any event, treatment directed against the thyroid gland successfully reduces serum calcium to normal levels.

Manifestations of hypercalcemia are assuming an ever-increasing importance in the natural history of malignant disease, so much so that serum calcium determinations should now be considered an integral part of the routine work-up of any patient with a disseminated malignancy. The search for hypercalcemia in these patients is not simply a matter of diagnostic nicety—it is essential, for more pressing reasons. Hypercalcemia is often missed because the symptoms it produces are too easily and too often attributed to the underlying neoplasm. In addition, since effective therapy is available, undiscovered hypercalcemia may, in itself, be needlessly disabling or life-threatening to these already burdened persons.

Included loosely in our classification, under tumors involving the bone marrow, are those patients afflicted with multiple myeloma, leukemia, Hodgkin's disease and a variety of lymphomas. Presumably, in these disorders the hypercalcemia results from an increased rate of dissolution of bone trabeculae, even though roentgenographic evidence of bone destruction may not be demonstrable. The following case report is illustrative.

CASE 5.—*Mucoepidermoid carcinoma with hypercalcemia.*

C. P. (P.–St. L. H. #584747), a 44-year-old white plumber, was admitted in December 1955 because of frequent attacks of "gas pains" and a dull constant ache in the interscapular area of 2 weeks' duration. He vomited for the first time on the day of admission, but further questioning elicited symptoms of frequent nausea, lethargy, headache, constipation, dry mouth and polyuria. Past history was of interest in that, because of nephrolithiasis, pyelonephritis and hydronephrosis, the left kidney had been removed 14 years previously. Frequent checks since that time failed to show any progression of similar disease on the right. Physical examination was unremarkable except for moderately severe dehydration. Initial serum calcium, phosphorus and alkaline phosphatase values were 15.0 mg. %, 7.6 mg. % and 15.3 units, respectively. Blood NPN was 82 mg. %, and the patient excreted no PSP 15 minutes after injection. A complete bone survey revealed only questionable diffuse decalcification in the tibiae.

Despite a large fluid intake, the serum calcium level rose to 19.5 mg. %. The patient was given a slow infusion of 12 Gm. of sodium citrate, but the following day the serum calcium level remained at 19.7 mg. %. Repeated intravenous drip infusions, each containing 3 Gm. of edathamil calcium disodium (EDTA) (calcium disodium Versenate) were then administered over the next 3 days, with a resultant fall in serum calcium to 13.4 mg. %.

A tentative diagnosis of carcinoma of the parathyroids was made, and a neck exploration was carried out. No parathyroid tumor was discovered, but tissue fragments were found to contain mucoepidermoid carcinoma of undetermined origin. The patient expired on the second postoperative day.

At autopsy the diagnosis of mucoepidermoid carcinoma was confirmed. Metastases were widely spread in cervical tissues, mediastinum, heart, lungs and other tissues. Of particular interest was the fact that sections of bone showed a heavy and diffuse infiltration of the marrow by sheets of tumor cells. In addition, there were diffuse areas of calcification in the papillary regions of the remaining kidney.

Comment.—The diagnosis of hypercalcemia in this patient was based on the aggregation of symptoms alone; but the finding of disseminated carcinoma came as something of a shock, since x-ray examination showed the bones to be essentially normal. The use of edathamil calcium disodium is discussed in a later section, but our inability to completely abolish the hypercalcemia with massive doses serves as a rough gauge of the tremendous rate of bone dissolution that must have been occurring in this patient.

Adrenal steroid therapy was not employed in this patient because, at the time, we were not aware of its efficacy in combating hypercalcemia from any cause other than primary hyperparathyroidism.

The appearance of hypercalcemia in patients with carcinoma of the breast metastatic to bone is now a medical commonplace (17), and the same complication is being reported with increasing frequency in association with metastatic tumors of almost every description. The occurrence of hypercalcemia is so common that reliance on clinical acumen alone to screen suspects is no longer defensible; every patient with metastatic carcinoma should have serum calcium concentrations measured *at regular intervals.*

Case 6.—*Carcinoma of the breast with bone metastases and hypercalcemia.*

M. Z. (P.–St. L. H. #600412), a 56-year-old white woman, was admitted in February 1957. She had a right radical mastectomy for adenocarcinoma in 1948, and the left breast had been removed in 1953. In May 1955 she was found to have metastatic involvement of the mediastinum, right pleura and left iliac crest. A bilateral adrenalectomy was performed in July 1955, and she was maintained on cortisone, 50–75 mg. per day, after that time. On admission, complaints of severe bone pain, dyspnea and fatigue overshadowed symptoms referable to hypercalcemia except, perhaps, for a dry, bitter taste in the mouth.

Roentgen examination revealed metastatic lesions in the left and right lower ribs, vertebrae and right scapula, along with a widened mediastinum and bilateral pleural effusions. The initial serum calcium value was 18.1 mg. %; blood NPN was 66 mg. %. Subsequent values are shown in Figure 3. It is evident that the adrenocorticoid therapy, increased over previous maintenance levels, was accompanied by a steady fall in serum calcium to normal values. Interestingly, in this and other hypercalcemic patients, we have frequently noted that, as the serum calcium falls, a hypophosphatemia appears.

Despite the relief of the hypercalcemia attributable to the adrenal steroid therapy, the patient's general response was poor, and she expired 36 days after admission.

The necessity to guard against unsuspected hypercalcemia is especially important whenever a change in the therapeutic regimen is contemplated. Hormonal treatment of carcinoma of the breast remains empiric, but, nonetheless, quite effective, in a sizable segment of the patient population (18). However, androgen

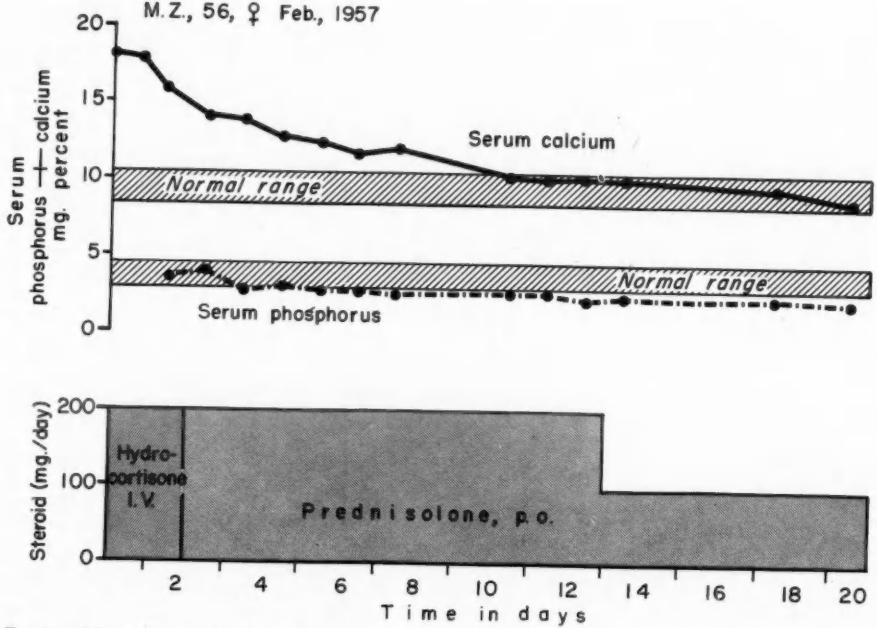

FIG. 3.—Effect of adrenocorticoids on hypercalcemia associated with carcinoma metastatic to bone.

Time in days

FIG. 3.—Effect of adrenocorticoids on hypercalcemia associated with carcinoma metastatic to bone.

or estrogen therapy may, quite unpredictably, precipitate or intensify hypercalcemia to an alarming degree (7). It is reasonable to assume that this aberrant response results from an exacerbation of the tumor-induced osteolytic process; and, indeed, the measurement of the concurrent hypercalciuria has been recommended as an indication of the advisability of continuing the regimen initiated. This view, however, has been challenged, and it is certainly true that some patients ultimately respond to hormonal treatment which is continued in the face of an early, temporary "flare." The history of a patient whose course illustrates some of these points is summarized later (Case 15).

A more recently emphasized and rather fascinating development in this area is the discovery that patients with malignant tumors may manifest *hypercalcemia without any apparent involvement of bone.* The syndrome has been observed in patients with neoplasms of the lung, kidney or ovary (12). Of especial interest is the fact that the hypercalcemia promptly disappears following the removal of the primary tumor, leading to the plausible hypothesis that the neoplasm produces (or stimulates the production of) a parathyroid-like hormone.

Nonneoplastic disease of bone may also be associated with hypercalcemia, the classic example being Paget's disease. In this disorder, the active disease process is reflected in the great increases in serum alkaline phosphatase activity. In two recently observed patients, the serum alkaline phosphatase value was 82 units in one and 136 units in the other! These values are interpreted to indicate that, in active disseminated Paget's disease, the uptake of calcium by bone proceeds at an extraordinarily rapid rate. For this reason, physical inactivity, which apparently depresses the *accretion* of calcium by bone, is particularly likely to provoke hypercalcemia in these patients as well as others in whom a tendency toward hypercalcemia is present (*see acute osteoporosis,* on page 26).

Careful documentation of hypercalcemia in the peculiar disease known as *polyostotic fibrous dysplasia* (2) is not available, but we have seen a patient (S. D., P.–St. L. #627835) in whom there is evidence that hypercalcemia existed in the past. The diagnosis was established by typical roentgenographic findings, as well as by bone biopsy. Although serum calcium levels were repeatedly nor-

mal and careful evaluation of parathyroid activity (15) was unrevealing, the patient had well-demarcated calcification in the renal papillae by x-ray examinations. It was concluded that, at some time in the past, perhaps when the bony abnormalities were more actively progressing, this patient was subjected to a period of elevated serum calcium concentration (at least, of the ionized fraction), with resultant renal calcinosis. The patient's status has been re-evaluated regularly, and no evidence of progression of either the osseous or kidney lesions has been demonstrable.

As indicated previously, a reduced rate of bone synthesis, at a time when bone breakdown is proceeding at a normal or increased rate, may lead to an accumulation of Ca^{++}, with a consequent elevation in the serum. The example most frequently used to illustrate this point is that of the *acute osteoporosis of disuse*. The hypercalcemia is more likely to occur in children or young adults who have been acutely immobilized, either because of imposed restraint, such as a body cast, or because of paralytic difficulties, as in acute poliomyelitis.* These patients are easily subject to a negative calcium balance with hypercalciuria, and renal calculi commonly occur. A regrettable story is that of the youngster who fractures a femur or humerus and is heavily casted. A film of the fracture site reveals a local demineralization (local osteoporosis), and the child is listless, anoretic and complains of attacks of nausea with occasional vomiting. The concerned, but misguided, physician attempts to improve healing by administering calcium and vitamin D! The resulting hypercalcemia may be disastrous.

Despite the lack of any direct experimental support, it was deemed advisable to consider that the hypercalcemia of *adrenal insufficiency* also results from decreased bone synthesis, since osteoporosis may complicate the course of these patients; and there is no evidence to suggest an increased rate of bone breakdown. The coincidence of hypercalcemia and Addison's disease has been documented (10). However, its appearance may be, in part, due to hemoconcentration, since it occurs in association with Addisonian crisis when the plasma volume is reduced. The serum calcium is only mildly elevated, and the problem is dwarfed by the urgent

*Recent studies (Heany, R. P., Proc. Central Soc. Clin. Res. 33:46, 1960) indicate that accelerated bone breakdown may be more important here.

need to treat the primary disorder. Therapy adequate to relieve the adrenal insufficiency also restores the normocalcemic state.

A curious, related phenomenon is the constant hypercalciuria and the occasional hypercalcemia which appear during *acute withdrawal of adrenocorticosteroids*, either following adrenalectomy for Cushing's syndrome (8) or following the abrupt decrease or discontinuance of long-term adrenal steroid therapy. This change in calcium metabolism is part of a poorly defined, but quite real, "steroid-withdrawal syndrome," characterized most prominently by malaise, arthralgia, nausea and rather profound weakness. The hypercalcemia is apparently relatively innocuous and abates, along with the other manifestations, when the steroid dosage is increased and then followed by a program of gradual steroid reduction until the patient is finally weaned from the drug.

Hypocalcemia

The same factors which are instrumental in the production of hypercalcemia result, not unexpectedly, in hypocalcemia when operating in reverse. However, it should be mentioned that, theoretically speaking, all the clinical entities to be discussed here (with the exception of primary hypoparathyroidism) reflect some degree of secondary hypoparathyroidism. Any metabolic imbalance leading to a lowering of serum calcium ions should inevitably provoke an outpouring of parathyroid hormone, which in turn should release additional bone calcium until normocalcemia is restored. If this were so, only in the very rare instance when the relatively huge calcium reservoir in bone is exhausted should hypocalcemia eventuate. This apparent discrepancy remains unresolved; but it may well be that there are occasions when the parathyroids, like the pancreatic islets, the adrenal cortices and probably other endocrine organs, have a limited reserve or potential which is exceeded by the metabolic demands.

Chronic reduction in intestinal absorption of calcium is a common offender in the genesis of hypocalcemia and is often accompanied by osteomalacia, a term which has come to mean the bone disease resulting from an over-all long-standing calcium deficiency (2).

A time-honored cause of hypocalcemia, stemming from im-

paired absorption of calcium from the intestinal tract, is *vitamin D deficiency;* and the classic example is, of course, simple rickets, i.e., an actual lack of exposure to vitamin D. It is often said that in our vitamin-conscious culture the likelihood of finding a rickety child is almost nil. However, those who see patients in large urban areas are not so sanguine, as the following case report attests.

CASE 7.—*Simple rickets.*

C. A. (P.–St. L. H. #013517), a 24-month-old Negro boy, was admitted because of inability to stand properly or to walk. He was also noted to have poor general physical development. He was not able to talk, but he seemed alert and happy. The past history revealed that he disliked milk and took less than 1 cup per day. He had never taken milk from a bottle, and he had been breast fed for 23 of his 24 months and had never been given any vitamin supplements. There had been no other significant illnesses. The mother was apparently healthy; and the patient had four living siblings, aged 11–18 years.

Physical examination revealed a small child in no distress but with prominent enlargement and thickening in the area of both wrists and ankles. There was slight bowing of the tibiae and prominence of the tibial trochanters. The size and shape of the head were normal; the fontanelles were closed. Only three teeth were present, all being incisors. The chest showed a typical ricketic rosary with a symmetrical distribution. No other abnormalities were noted.

Roentgenograms of the hip joints, wrists and tibiae (Fig. 4, *A*) showed destruction of the metaphyseal ends of all long bones, with marked decalcification and some periostitis. The serum calcium value was 8.7 mg. %; serum phosphorus, 3.1 mg. %. The alkaline phosphatase value was 49.2 units. A quantitative 24-hour urinary calcium study revealed a total of 5.2 mg. per 24 hours. A repeat determination several days later showed 4.5 mg. per 24 hours; %TRP was only 55.

The patient was placed on a high calcium diet and only 5,000 units of vitamin D per day. Despite this modest dose; clear-cut evidence of healing was evident 15 days later, when the x-ray appearance of his bones was re-examined. (Fig. 4, *B*).

Comment.—This patient provides one of the very few arguments that can be mustered against the practice of breast feeding. A change to cow's milk enriched with vitamin D would have been beneficial. Serum calcium levels were borderline low, while the serum phosphorus value of 3.1 mg. %, normal in an adult, is definitely low in a 2-year-old child.

It should be emphasized that not all patients with rickets have hypocalcemia; perhaps its occurrence depends on the degree of parathyroid unresponsiveness.

The entity of *vitamin D resistant rickets* has recently been sub-

FIG. 4.—Effect of vitamin D on rickety bones: (*A*) before and (*B*) 15 days after 5,000 units per day (see Case 7).

jected to a reappraisal which has raised the question whether an actual "resistance" to the action of vitamin D ever really occurs. There are well-documented reports (20) of patients with a hereditary form of osteomalacia, in whom very large doses of vitamin D are required for bone healing. However, these individuals have been shown to have a renal tubular lesion, which probably ac-

counts for most or all of their difficulties (see *phosphate diabetes*, on page 42). Nevertheless, there are rare patients in whom osteomalacia develops apparently because of an inordinately great requirement for vitamin D. We recall seeing a 2-year-old boy with bowed legs and with x-ray findings pathognomonic of rickets. He had been given adequate doses of cod-liver oil almost continuously since the age of 6 weeks. With an increase in dosage of vitamin D and calcium, he made a complete recovery. These patients may or may not have hypocalcemia; our patient did not.

A variety of intrinsic mucosal defects in intestinal absorption may give rise to hypocalcemia. These include *idiopathic steatorrhea, lymphoma of the bowel, Whipple's disease, Zollinger-Ellison disease* and other conditions. The two following patients have been selected to serve as illustrative examples:

CASE 8.—*Idiopathic steatorrhea.*

M. G. (P.–St. L. H. #655228), a 34-year-old Mexican housewife, was admitted in February 1960 with a history of frequent (4–5 per day), large, often foul-smelling, bowel movements extending over 12 years and associated with considerable weight loss and weakness. For the previous 9 years, she had frequent episodes of "stiffness," tingling and numbness in her hands and feet with muscle cramps. She was told that she had low blood calcium and took a calcium preparation with temporary relief. She never had convulsions, but on two occasions she had severe typical carpal-pedal spasm with alarming laryngeal stridor. There gradually appeared moderate hair loss, dry scaly skin and brittle nails.

Physical examination showed the following: Blood pressure was 105/50. The tongue was beefy red, and body hair sparse, and the skin and nail changes mentioned above were confirmed. A tender liver edge was palpable 3 fingerbreadths below the right costal margin. There was marked generalized muscle weakness, and both the Trousseau and the Chvostek signs were present.

A rather elaborate array of laboratory procedures confirmed the impression of intestinal malabsorption. The patient had a moderately severe iron deficiency anemia (Hgb, 8.1 Gm. %; serum iron, 25 μg.%). The oral glucose tolerance test was flat, but the intravenous glucose tolerance was normal. After the ingestion of 25 mg. of xylose, the serum xylose level was 12.9 mg. % (normal: 33–58 mg. %) 2 hours later, and 1.1 Gm. of xylose (normal: 6–10 Gm.) was excreted in the urine in 5 hours. Ninety and 46% of the ingested doses of I^{131}-labeled triolein and oleic acid, respectively, were excreted in the stool, in contrast with the

normal excretion of less than 2%. Serum electrophoresis revealed hypoalbuminemia (3.3 Gm. %), with total protein, 5.8 Gm. %. Prothrombin time was greatly depressed (15%) but responded promptly to parenteral vitamin K (82%). Serum electrolytes, particularly potassium, were low (in mEq./L.: Na 134, Cl 88, K 2 and CO_2 28). Prior to treatment, the serum calcium and phosphorus values varied between 6.8 and 7.9 mg. % and 1.0 and 1.4 mg. %, respectively; the serum magnesium was 1.24 and 1.42 (normal: 1.48–2.08) mEq./L. Although the percentage of renal tubular reabsorption of phosphate was normal (89.5), the phosphate clearance was low (5 ml./min.). As expected, the 24-hour urinary calcium excretion was very low (11.7 mg.). X-ray examination revealed a "deficiency state" small-bowel pattern and normal bone density. An electrocardiogram showed prolongation of the Q–T interval.

Despite sizable doses of oral vitamin D (50,000 units daily), dihydrotachysterol and calcium gluconate, the patient had repeated attacks of hypocalcemia. Finally, she was given one dose of an intravenous preparation, Vi-De 3 Hydrosol (Wander Co., Bern, Switzerland), containing 600,000 units of vitamin D and the attacks abated. She was placed on a gluten-free diet, to which she responded in a most gratifying fashion. After only 35 days of diet therapy, the patient had gained 19 pounds, was completely symptomless, and all the laboratory procedures described above had returned to normal. She has remained in remission since discharge.

Comment.—This patient presents a "textbook picture" of nontropical sprue (idiopathic steatorrhea) responsive to a diet free of wheat products. The metabolic studies were also typical with, perhaps, one exception worth mentioning. It has been shown that the clinical effects of hypocalcemia are ameliorated or abolished in the presence of low serum potassium levels. For this reason, it was surprising that our patient suffered rather severe tetany, since she did have clear-cut hypokalemia, from which a protective effect might have been anticipated.

CASE 9.—*Steatorrhea secondary to Hodgkin's disease of the small intestine.*

F. S. (P.–St. L. H. #596366), a white housewife, was first hospitalized in March 1955 at age 53, because of frequent episodes of cramping, numbness and tingling of the hands, feet and about the mouth during the preceding 5 years. She also had had attacks of diarrhea with up to 12 bowel movements per day. During these episodes, the feces were liquid, foamy and foul smelling. Two years previously she had noted the appearance of a firm mass in the right side of her neck. She was

anoretic and had lost 15 pounds in the previous 6 weeks. Physical examination revealed generalized lymphadenopathy. A biopsy of a right cervical node revealed an infiltration, compatible with Hodgkin's disease. The serum calcium value was 4.4 mg. %; the serum potassium, 3.3 mEq./L.; and roentgenographic studies of the bowel revealed a "flattening of the mucosa of the entire intestinal tract from the duodenum through the colon. The wall of the small intestine is markedly thickened." The findings were interpreted as being compatible with lymphoma of the intestinal tract.

The patient was given a course of nitrogen mustard, with a resultant increase in the serum calcium value from 4.6 to 9.0 mg. % in 26 days. The serum phosphorus level, which was 3.2 mg. % on admission, fell to 1.8 mg. %. Along with the abatement of the spruelike symptoms and the attacks of tetany, the lymph-gland enlargement disappeared. She was maintained on varying doses of prednisone, and in the ensuing 18 months she was rehospitalized on three occasions for recurrences of frank tetany. Relief was obtained once by an additional course of nitrogen mustard therapy and twice by increasing the steroid dosage.

The patient has done very well during the past 4 years on small maintenance doses of prednisone.

Comment.—This patient presented with symptoms quite similar to those in Case 8. Here, however, malabsorption was caused by granulomatous infiltration of the small bowel, and a complete remission was obtained with the use of nitrogen mustard therapy. It is of particular interest that adrenocorticoids, which are frequently used to treat hypercalcemia, were successfully used in this case to relieve hypocalcemia, presumably by improving intestinal absorption.

Other causes of poor absorption from the gut, such as *chronic biliary obstruction, intestinal shunts* (resulting from extensive small bowel resections, *gastrocolic fistula* (or inadvertent surgical gastroileostomy) or simply *rapid transit of intestinal contents* may or may not provoke hypocalcemia. Clearly, in all these disorders of the gut, impaired assimilation of calcium is due, not only to inherent mucosal defects, but also to the formation of poorly absorbed calcium soaps in the intestinal lumen and decreased absorption of fat-soluble vitamin D.

Hypocalcemia from depressed dissolution of bone stems from hypoparathyroidism in one form or another; and, of those listed in the classification, *idiopathic hypoparathyroidism* exemplifies

this disease in its purest form. The cause of this unusual disorder remains enigmatic, since it is difficult to conceive of a pathologic process that would lead to the loss of function of four discrete glands in an otherwise healthy individual. Perhaps an autoimmune destructive process, analogous to that leading to Hashimoto's thyroiditis, is operative in these patients. A typical case is summarized below:

CASE 10.—*Idiopathic hypoparathyroidism.*

D. S. (P.–St. L. H. #620940), a 27-year-old white housewife, was admitted to the Rice Metabolic Unit of the Presbyterian–St. Luke's Hospital for study in September 1958. About 2 years previously, the patient began experiencing attacks in which there was a sudden "drawing-in of arms and hands" with local numbness and tingling. These episodes lasted several hours and occurred at approximately 2-week intervals. She also discovered that stiffness and twitching of her feet ensued after sitting with her legs crossed. More severe attacks began with some exertional dyspnea and a nonproductive cough, followed by stiffness extending from the occiput to the legs. The toes would cramp (flex), forcing the patient to walk on her heels. Her eyeball muscles twitched, and her voice became hoarse. These episodes occurred at 2- to 3-month intervals and lasted about 2 days. There was no history of neck surgery, grand mal seizures or blurred vision. However, the patient had become aware of increasing dryness of the skin and hair, with some brittleness of the nails. Physical examination was distinguished chiefly by strongly positive Chvostek and Trousseau signs. Slit-lamp examination failed to reveal any lenticular opacities, and roentgenograms of the skull were negative for calcification of the basal ganglia. Nor did a bone survey reveal any abnormal bone density or ectopic calcification elsewhere. Electrocardiograms and an electroencephalogram were normal. The serum calcium value was 4.5 mg. %; phosphorus, 5.2 mg. %; and alkaline phosphotase, 1.4 units. Phosphate clearance was only 4.4 mg. per minute, while the percentage of renal tubular reabsorption of phosphate was 97.

This patient has remained symptom-free since discharge, although a positive Chvostek sign can often be elicited. Serum calcium and phosphorus levels have been checked at monthly intervals and have ranged from 8.0 to 9.5 mg. % and from 3.5 to 4.6 mg. %, respectively. As indicated in the discussion of Case 1, it has been necessary at times to vary treatment to attain this degree of control, but usually the patient is maintained on 75,000 units of vitamin D and 6 Gm. of calcium lactate per day.

Comment.—This patient's story of "shortness of breath" and cough with tetanic attacks represented laryngeal stridor, since it is known that the inspiratory distress of laryngospasm may be confused with cardiac asthma (16).

An intriguing variant of this disorder is what the distinguished endocrinologist, Fuller Albright, has called *pseudohypoparathyroidism* (1), since his studies revealed that, in these patients with hypocalcemia and hyperphosphatemia, the renal tubules apparently are insensitive to the phosphoruretic effect of parathyroid hormone; and in one patient, biopsy revealed parathyroid hyperplasia rather than an absence of parathyroid tissue. The pathogenesis of this entity remains puzzling, however. If the parathyroid glands are really stimulated, why is there no hypercalcemia resulting from enhanced bone breakdown? Elevated serum calcium levels have never been reported; but several patients have shown striking bony demineralization, so that there may, indeed, be increased resorption of bone. Patients with pseudohypoparathyroidism have surprisingly uniform abnormalities of stature and characteristically short metacarpals, resulting in the "dimple sign" when the hand is clenched. Dr. Albright has also found patients with the bony stigmata of pseudohypoparathyroidism but with normal serum calcium and phosphorus levels; these patients he has dubbed "pseudo-pseudohypoparathyroid."

In this connection, one of us (TBS) saw a patient who had the mental deficiency, round face and short neck suggestive of pseudohypoparathyroidism. When the serum calcium and phosphorus were found to be consistently normal, the diagnosis of pseudo-pseudohypoparathyroidism was entertained. Alas, roentgenograms of the bone disclosed no abnormalities. There remained only the face-saving gesture of declaring that the patient had "pseudo-pseudo-pseudo (or pseudo^{3})" hypoparathyroidism! This admittedly irrelevant (and irreverent) observation is offered as an extension of Dr. Albright's spirit, if not his perspicacity.

The majority of persons suffering from hypoparathyroidism owe their disease to surgical intervention, either knowingly, following bilateral radical neck dissection (as in Case 1), or inadvertently, as in the following unusual patient, who suffered total removal of the parathyroids.

CASE 11.—*Postsurgical hypoparathyroidism with delayed onset and bony demineralization.*

H. S. (P.–St. L. H. #597696), a 65-year-old married scrubwoman, was first admitted, at age 34, in April 1927 with persistent menorrhagia and symptoms and signs of a toxic nodular goiter. She underwent a vaginal hysterectomy and, 1 year later, a subtotal thyroidectomy. Recovery was uneventful with no evidence of hypothyroidism or hypoparathyroidism. Eleven years later, in April 1939, she had a bout of syncope associated with what was thought to be exertional dyspnea (?laryngospasm), for which she was digitalized. Two years after this, a second episode of sudden loss of consciousness occurred while the patient was lying in bed.

In March 1942, 14 years after the thyroidectomy, the patient was admitted to the Cook County Hospital because of a sudden attack of precordial pain, leading to a spell of unconsciousness lasting 20 minutes. One month previously, she had noted the onset of "hot flashes," fatigue, dyspnea, nervousness, mild ankle edema and mental depression. Physical examination revealed obesity, slight exophthalmos on the right side and bilaterally positive Chvostek signs. Laboratory findings disclosed albuminuria, slightly elevated NPN, hypocalcemia and hyperphosphatemia with normal alkaline phosphatase. She suffered two additional similar attacks during the same year, but then remained relatively well, taking only calcium lactate. Her course from 1946 to 1960 was rather complex; but several points are worth emphasizing: First, despite reasonable care, her serum phosphorus level remained elevated and serum calcium values showed wide fluctuations, alternating between tetanic and toxic levels. Second, while roentgenograms revealed normal bone density in 1947, minimal demineralization was detected 5 years later and, after 8 years, a striking decrease in bone density with multiple compression fractures of the spine was evident. And third, no repair of the osseous lesions could be detected despite treatment with vitamin D, calcium gluconate and an estrogen-androgen mixture, although associated bone tenderness was considerably improved.

Intensive studies of the renal handling of phosphate supported the conclusion that the patient had hypoparathyroidism in the presence of mild renal impairment. In March 1960 she fell and suffered an intertrochanteric fracture of the neck of the right femur. Following the insertion of a Smith-Peterson nail, her condition deteriorated progressively and she died 6 days later. At autopsy, very careful examination failed to reveal the presence of any parathyroid tissue. The right ovary was intact and there was only mild nephrosclerosis. The bones showed an abnormal trabecular pattern and increased osteoclastic activity.

Comment.—This patient is quite remarkable for two reasons: (1) after surgical removal of the parathyroids, there was a latent period of at least 11 years before manifestations appeared, and these occurred at the time of probable menopause; and (2) the obvious hypoparathyroidism was associated with severe bony demineralization. Both of these phenomena have been described before, but not in the same person. It should also be mentioned that, in this patient, loss of consciousness apparently without grand mal seizures occurred as an initial symptom and, again, tetanic symptoms sometimes simulated those of cardiac disease.

Probably the commonest form of hypoparathyroidism is that which results from *temporary damage or partial removal of parathyroids* after neck surgery. Usually symptoms appear soon after surgery and last from a few days to several weeks. Treatment with calcium preparations alone usually suffices; and it is preferable to avoid medication with vitamin D, since intoxication may supervene as the patient recovers. If recovery is delayed for longer than 3 weeks, the likelihood is that the damage is permanent. However, there are exceptions, as illustrated by this next case.

CASE 12.—*Postsurgical hypoparathyroidism with delayed recovery.*

B. M., a 54-year-old widow, was first seen as an outpatient in November 1958. Because a thyroid nodule had been found, a subtotal thyroidectomy had been performed 3 weeks previously. Three days postoperatively, she noted numbness and tingling of her hands with positive Trousseau and negative Chvostek signs. Serum calcium and phosphorus values were 6.7 and 5.5 mg. %, respectively. She was treated with calcium gluconate, dihydrotachysterol and calciferol. Five days later, the serum calcium value was 7.5 mg. % and the phosphorus value, 4.9 mg. %. Hypocalcemia and hyperphosphatemia persisted, despite medication, for 6 weeks postoperatively. She then became asymptomatic; but 4 months postoperatively she became intoxicated, with a serum calcium value of 12.8 mg. %. One month later the serum calcium value was 8.2 mg. %, and treatment was resumed. The following month, 6 months postoperatively, the serum calcium value was 8.3 mg. %. However, hypercalcemia again supervened, and therapy was permanently discontinued. The patient has been asymptomatic since. The most recent serum values obtained were: calcium, 9.7, and phosphorus, 2.9 mg. %.

Comment.—The reason for the inordinate delay in this patient's recovery from temporary postoperative hypoparathyroidism

has not been elicited, but her course points up the necessity for careful follow-up.

Following the removal of a parathyroid adenoma, particularly in the presence of bone disease, postoperative hypocalcemia may be severe and require energetic therapy, as illustrated in Case 3. Complete recovery is the rule. However, the following case report indicates that recovery may not always ensue.

CASE 13.—*Permanent hypoparathyroidism following removal of a parathyroid adenoma.*

M. S. (P.–St. L. H. #660079), a 51-year-old woman, was admitted in June 1960, primarily for a right chronic otitis media and a cholesteatoma. However, there was a history of renal stones, with colic beginning 22 years previously, and requiring lithotomy on two occasions. In 1950 the diagnosis of hyperparathyroidism was made, and an exploration of the neck revealed a parathyroid adenoma which was successfully removed. Postoperatively, because of tetanic manifestations, the patient was treated with varying doses of dihydrotachysterol. Since that time, she has had frequent episodes of nervousness, light headedness, weakness and muscle cramps. Pressure applied to the arms resulted in spasm, numbness and tingling of the hands. Ten years after the removal of the adenoma, the serum calcium value was 7.0 mg. %, the serum phosphorus, 5.0 mg. %, and the percentage of renal tubular reabsorption of phosphate was 95. An electroencephalogram showed "bitemporal spike seizure activity." With increased dihydrotachysterol therapy, the serum calcium level gradually rose and the serum phosphorus values varied, so that, at the time of discharge, 24 days later, the respective values were 9.0 and 5.9 mg. %.

Comment.—This apparently permanent hypoparathyroidism, following the removal of a parathyroid adenoma, is very unusual and quite unexpected. The possibility that normal parathyroid glands were also removed at operation seems unlikely. More plausible possibilities are that the adenoma represented all the parathyroid tissue the patient had, or that the remaining parathyroid glands never recovered from the suppressive effects of the hypercalcemia previously induced by the adenoma.

Infantile tetany is a transient disorder presumably due to a relative deficiency in parathyroid function. Its occurrence is almost entirely confined to bottle-fed babies and may well be related to the fact that cow's milk is appreciably higher in phosphate content than is human milk.

The phenomenon of unusually rapid bone synthesis, graphically described as "hungry bones," may be expected when a chronic severe osteolytic process is abruptly terminated. The ensuing reparative osteoblastic activity may be so intense that the available calcium supply is insufficient and hypocalcemia appears. This is more likely to occur if the previous bone destruction has resulted in hypercalcemia with a resultant depression of parathyroid function. Removal of a parathyroid tumor in a patient with osteitis fibrosa generalisata satisfies these conditions, and the course of Case 3 demonstrates this point well.

Osteoblastic metastatic bone disease may also serve to provoke hypocalcemia. This phenomenon may occur spontaneously, but more often it appears during a rapid regression of osseous lesions. The following patient, who has been selected to illustrate this point, is of particular interest because her course exemplifies hypercalcemia, induced by estrogen, hypercalcemia relieved by adrenal steroids, and hypocalcemia resulting from (1) a tumor regression induced by adrenalectomy and (2) functional hypoparathyroidism secondary to the previous hypercalcemia.

CASE 14.—*Metastatic carcinoma of the breast: hypocalcemia during regression.*

L. T. (P.–St. L. H. #592842), a 62-year-old white female English professor, was admitted in April 1956 with a history of carcinoma of the right breast, discovered 10 years previously. Following radical mastectomy there was no recurrence until 1954, when a second carcinoma was found in the left breast. Again, a radical mastectomy was performed. In November 1955 a biopsy of a left supraclavicular node revealed a metastatic tumor; and, shortly after this, the patient noted low back pain, radiating to the pelvis and knees. Aside from the bilateral mastectomy scars and the secondary lymphedema of both arms, physical examination was not remarkable. X-ray examination revealed metastases in the skull and the thoracic and lumbar vertebrae. The serum calcium and phosphorus values were 10.9 and 4.7 mg. %, respectively. Alkaline phosphate activity was 10.7 units. These values are designated as "day 1" in Figure 5. Local x-ray therapy was started, and the patient was given large doses of diethylstilbestrol. On day 8, 3 days after discharge from the hospital, the patient noted marked lethargy, generalized weakness, anorexia and weight loss eventually totaling 7½ pounds. She was readmitted on day 14. The serum calcium value was found to be 17.0 mg. %. Stilbestrol

FIG. 5.—Effect of estrogen, adrenal corticoids and adrenalectomy-induced regression on serum calcium and phosphorus values (see Case 14).

was discontinued and large doses of prednisolone were administered, with a rapid fall in serum calcium to normal levels. This was accompanied by a fall in serum phosphorus from borderline elevated values. On day 25, a bilateral adrenalectomy was carried out; and, despite the administration of large quantities of calcium gluconate, the serum calcium level fell progressively to a low of 6.7 mg. %, while serum phos-

phorus fell to 1.5 mg. %. Indicative of the rapid new bone synthesis was the rise in the serum alkaline phosphatase value to 49.2 units. On the other hand, the possibility that relative hypoparathyroidism was also a contributory factor to the hypocalcemia is supported by the finding, on day 39, of a very low phosphate clearance (2.2 mg. per ml.) and a high percentage of renal tubular reabsorption of phosphate (99%). Dihydrotachysterol was started on day 38, and the serum calcium returned to the normal range, along with a progressive increase in serum phosphorus. Alkaline phosphatase levels remained elevated. The patient later showed unquestionable clinical and roentgenographic evidence of regression of the metastatic malignancy.

Excessive loss of available calcium has also been established as a cause of hypocalcemia. Excessive urinary excretion has been found in a variety of renal tubular diseases, all of them rather rare. In *renal tubular acidosis,* the kidneys are deficient in their ability to excrete an acid urine. This excessive retention of hydrogen ions results in metabolic acidosis and, for reasons not clearly understood, calcium and/or potassium wasting. Usually, other renal tubular functions are intact, although renal glycosuria may be present. Symptoms are similar to those of other cases of hypocalcemia, but occasionally the paresis of hypokalemia may dominate the clinical picture. Fortunately, there is usually no associated azotemia and the lesion is not progressive, so that an excellent response may be obtained by prescribing an alkalinizing salt mixture (see Case 4).

The term *Fanconi syndrome* refers to a much more extensive lesion of the renal tubules which results in many metabolites of widely differing properties being lost in the urine. The majority of cases are hereditary in nature, and the clinical manifestations usually appear in childhood. Even more rarely, the syndrome may also occur in an acquired form secondary to such diseases as *multiple myeloma, osteogeneic sarcoma* and, probably, *cystinosis.* In the patient whose history is summarized below, the apparent cause was *glomerulonephritis.*

CASE 15.—*Fanconi syndrome secondary to glomerulonephritis.*

M. C. (P.–St. L. H. #00736), a 54-year-old woman of Italian extraction, was first seen in our outpatient clinic 20 years ago because of menstrual irregularities; and 2 years later, a hysterectomy and bilateral oophorectomy were performed. Shortly thereafter, she complained of

pains in knees and legs, later accompanied by low back pain. She responded rather indifferently to salicylates. In 1950, 8 years after the onset of pain, roentgenograms of the pelvis showed generalized demineralization. The serum calcium and phosphorus values were 8.0 and 2.6 mg. %, respectively. In 1952, repeat x-ray examination disclosed several compression fractures of vertebral bodies, and bone pain continued. In 1954, following a fall, the patient sustained a fracture of her right hip, for which an arthrodesis was performed. By gradual progression, the bone and joint symptoms became so severe that by 1956 the patient had become bedridden. Physical examination revealed bone and joint pain with active or passive motion. The ribs, spine and all bony prominences were tender. Urinalysis revealed albuminuria and occasional glycosuria. The serum calcium value was 8.8 mg. %; the alkaline phosphatase, 29.5 units. In view of these findings a careful and complete bone survey was carried out (see Fig. 6). In all, 57 fractures and pseudofractures were counted!

When these additional findings, characteristic of Milkman's disease, were discovered, extensive metabolic studies were initiated. The patient was found to have slight azotemia (NPN of 45 mg. %), mild systemic acidosis (in mEq./L.—Na 144, Cl 115, K 3.4 and CO_2 20.2), and the urinary pH was fixed between 6.5 and 7.5. The serum levels of uric acid, glycine, alpha-amino nitrogen and creatinine were normal, but all these metabolities were excreted in prodigious quantities in the urine. Two-dimensional paper chromatography demonstrated that the amino-aciduria was generalized. The percentage tubular reabsorption of phosphate was only 47. Subsequent calcium and phosphorus determinations revealed levels as low as 7.4 and 2.2 mg. %, although tetany never supervened. Percutaneous renal biopsy revealed "chronic glomerulonephritis and questionable pyelonephritis."

During the ensuing 4 years the patient has been treated with vitamin D (50,000–100,000 units per day), calcium gluconate (3–6 Gm. per day) and Shohl's citric acid–sodium citrate mixture (see Case 4). Improvement has been steady and impressive. Bone pain and tenderness have completely disappeared, and the patient walks without difficulty using only a cane.

Comment.—It is worth emphasizing that the initial clue to the proper diagnosis in this case was the finding of a low serum phosphorus level in a patient who manifested mild glomerular insufficiency, which, if anything, should result in elevation of the serum phosphorus. Indeed, it is our contention that a persistently low serum phosphorus level demands explanation. It has always led

to the diagnosis of intestinal, renal or parathyroid disease, with the exception of occasional patients with diabetes or frank, exogenous malnutrition.

The puzzling feature of this case is the etiology of the renal lesion. Perhaps it is hereditary; the patient's father died of "kidney trouble." However, examination of the urine of close relatives

FIG. 6.—Pseudo-fractures of osteomalacia in patient with Fanconi syndrome (see Case 15).

failed to uncover any abnormalities. If the diagnosis is glomerulonephritis, as suggested by renal biopsy, it represents the first such instance of which we are aware.

Phosphate diabetes or "phosphate wasting" are terms more recently coined (5) for what has been widely referred to as "vitamin D–resistant rickets" (20). This disorder, clearly hereditary in na-

ture, is characterized by the stigmata of osteomalacia, which progresses unless large doses of vitamin D are given continuously. The primary lesion appears to lie in the renal tubules, which are incapable of conserving phosphate, with the result that urinary phosphate excretion remains excessive. Serum calcium levels are more often normal than low, but serum phosphorus levels are almost invariably low.

As in the Fanconi syndrome, phosphate diabetes may occur rarely in adults who can provide no evidence of familial disease. One such individual (A. G., P.–St. L. H. #634037) had normal serum calcium levels, but the serum phosphorus remained persistently in the range of from 1.6 to 2.4 mg. %. She was remarkable in her resistance to vitamin D intoxication. She could tolerate from 250,000 to 400,000 units of vitamin D plus 4 Gm. of neutral sodium phosphate daily, without manifesting any clinical or biochemical signs of hypercalcemia. Furthermore, doses of this magnitude were required to raise the serum phosphate to normal levels.

In order to complete our classification, it remains to discuss hypocalcemia which occurs, not because of deficient intake or excessive loss, but due to quantitative abnormalities in the chemical binding which effectively lowers extracellular calcium concentrations. A relatively uncomplicated example is that of *acute pancreatitis*. The release of pancreatic lipolytic enzymes into the peritoneal cavity results in autodigestion of the neutral fat of the omentum and the other tissues. The free fatty acids, thereby produced in large amounts, combine with extracellular calcium to form soaps, and the serum calcium falls. This hypocalcemia is rather evanescent, rarely lasting more than 24–48 hours, and is easily managed with intravenous calcium gluconate.

A greater potential threat is the reduction both in total serum calcium and the ionized fraction following the administration of toxic amounts of citrate during the course of *massive blood transfusions* (3). The citrate binds firmly to the calcium ions so that, even though the total serum calcium is normal, the ionized fraction may be greatly reduced. Later, because the calcium citrate complex is rapidly excreted, the total serum calcium also fails. Tetany occurs; but it is more frequent and more severe in children, since the dose of citrate is relatively large. Among adults,

patients with hepatic disease are more susceptible to citrate intoxication, since the liver plays an important role in the removal of citrate from the plasma. Also, in adults, citrate-induced hypocalcemia is apt to be associated with severe vascular collapse without clinical tetany, so that recognition of this complication and prompt treatment with calcium salts may be delayed or entirely overlooked.

A more recent arrival in the physician's armamentarium is the very powerful chelating agent, edathamil calcium disodium (EDTA). This compound binds ionized calcium so firmly that the calcium, so bound, is undetectable by the usual analytical technics. For this reason, the serum calcium level appears to fall precipitously after EDTA infusion (15). Therapeutically, EDTA has been used in attempts to remove excess calcium from ectopic sites, such as renal calcinosis and calcinosis universalis. Also, there is a current vogue for its use in the treatment of scleroderma. Finally, EDTA has a place in the emergency treatment of life-threatening hypercalcemia. The calcium level may be very rapidly reduced, but we have been disappointed to find that the serum calcium often returns to its original high level in 12–24 hours after an infusion is completed. Furthermore, chronic administration of EDTA itself may precipitate severe, and perhaps fatal, renal tubular degeneration, so that long-term use is contraindicated.

Hypoproteinemia, particularly that of the nephrotic syndrome, is often accompanied by hypocalcemia. This, however, usually stems from a decrease of calcium bound to plasma proteins; ionized calcium is normal. For this reason, the finding is relatively innocuous and the appearance of tetanic manifestation is very unusual.

Finally, the *hypocalcemia of chronic renal insufficiency,* perhaps the most common of all varieties, completes this survey. The metabolic events in uremia remain so complex that a full explanation of the genesis of the regularly occurring hypocalcemia is yet to be found. Since the serum citrate level (and that of other organic acids) is elevated in uremia, it is possible that there is excessive excretion of chelated complexes of calcium. Metabolic acidosis probably also is involved. The familiar cramps, muscle twitchings and convulsions of uremia are certainly related, at least

in part, to the associated hypocalcemia and need not be elaborated further.

In view of this rather extensive survey of diseases characterized by abnormal serum calcium levels, a formal elaboration of differential diagnosis will not be undertaken. Readers are referred to recent reviews (15, 19) for further discussion. For similar reasons, a separate discussion of therapeutic measures is not included. The necessity for directing treatment, whenever possible, at the underlying cause of the hyper- or hypocalcemia remains a fundamental guiding principle.

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